

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 52-82 were pending in the case at the time of the Office Action, with claims 1-51 having been previously canceled from the case without prejudice or disclaimer. In response to the Office Action dated April 19, 2006, no claims are being amended, no new claims are being added, and no additional claims are being canceled. Therefore, claims 52-82 are currently under consideration.

B. The Rejections Under 35 U.S.C. §103(a) Are Overcome

Claims 52-58, 61-66, 69, and 79 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Anderson *et al.* (Nucl. Med. Biol., 1995, Vol. 22, No. 2, pp. 165-172) in view of Auzeloux (J. Labelled Cpd. Radiopharm., 1999, Vol. 42, pp. 567-579). The Examiner argues that one of ordinary skill in the art would be motivated to combine reference teachings to lead to the claimed methods of imaging. Applicants respectfully traverse, and respond as follows.

1. Auzeloux *et al.* Is Not Prior Art

The *Manual of Patent Examining Procedure (MPEP)* §715.02, provides that “Applicant may overcome a 35 U.S.C. §103 rejection based on a combination of references by showing completion of the invention by applicant prior to the effective date of any of the references; applicant need not antedate the reference with the earliest filing date.”

Applicants have submitted a Declaration of Inventors under 37 C.F.R. §1.131 (Appendix A, hereinafter, “the Declaration”) to set forth facts demonstrating reduction to practice of the claimed methods of imaging a site within a subject prior to June 1, 1999. Auzeloux *et al.* was published in June, 1999. The above-referenced patent application claims priority to several patent applications, with the initial patent application in the chain of priority having a filing date of October 25, 1999 (USSN 09/434,313; now issued U.S. Patent 6,692,724).

Applicants have set forth facts in their Declaration establishing that they prepared compositions of particular radionuclide-labeled bis-aminoethanethiol (BAT) dicarboxylic acid-targeting ligand conjugates and detected radioactive signals by emission tomography in subjects following administration of the compositions to the subjects. Declaration, paragraph 5. The inventors synthesized the following conjugates and analyzed the imaging capabilities of these conjugates in rats : (1) ^{99m}Tc -ethylenedicysteine (EC)-folate; (2) ^{99m}Tc -EC-metronidazole (MN); (3) ^{99m}Tc -EC-nitroimidazole (NIM); (4) ^{99m}Tc -EC-pentaglutamate (GAP); (5) ^{99m}Tc -EC-Annexin V (ANNEX); and (6) ^{99m}Tc -EC-colchicine (COL). Declaration, paragraph 5, and Exhibit 1 of Declaration. Scintigraphic imaging and autoradiography studies were conducted using each of these imaging agents. *Id.*

Applicants point out that their affidavit, in order to overcome a rejection based on a combination of references, “must show possession of either the whole invention as claimed or something falling within the claim(s) prior to the effective date of the reference begin antedated.” Applicants submit that each of the embodiments of the claimed invention addressed in the Declaration at least fall within the scope of the claims, and thus, the Declaration is sufficient to antedate Auzeloux *et al.*

2. Anderson *et al.* Alone Fails to Obviate the Claimed Invention

In the absence of Auzeloux *et al.*, the claimed invention is not unpatentable. Applicants point out that the Examiner has withdrawn a rejection under 35 U.S.C. §103(a) based on Anderson *et al.* in view of Applicants’ response to the previous Office Action. Therefore, the Examiner has acknowledged that the claimed invention is nonobvious in view of Anderson *et al.*.

Applicants stand by their response to the Office Action dated November 4, 2005, where they addressed the deficiencies of Anderson *et al.* In particular, Anderson *et al.* makes reference to the observation that an indium complex with excellent *in vivo* stability “is desirable when

designing bifunctional chelates to be conjugated to larger molecules such as antibodies or peptides.” (page 165, col. 1) However, this statement does not identify any BAT conjugate *per se*, and, more importantly, the article itself suggests that it would be unpredictable whether a chelate conjugated to a protein or peptide would be stable *in vivo* (“the nature of the bifunctional chelate use to complex radiometals to proteins or peptides also alters the uptake and in clearance organs...” page 165, sentence bridging columns 1 and 2).

In the Conclusion section, the article states that “[i]t would be interesting to compare the biodistribution” of an indium labeled EC analogue conjugated to a “protein or peptide” or other indium labeled conjugates. (page 172, col. 2) However, the article further teaches the uncertainty of whether such conjugates would prove to have sufficient stability, noting that “[t]he accumulation of radiolabeled ligand complexes in the liver without clearance may be indicative of complex instability” and that “[t]his needs to be further investigated” (page 172, col. 1).

From the foregoing passages, it appears that the authors of Anderson *et al.* simply do not have any degree of certainty whether EC conjugates would be sufficiently stable to be useful. They merely state, in effect, that it would be “interesting” to find out the answer to this question. Accordingly, Anderson *et al.* is nothing more than an “obvious to try” reference. This type of rejection is improper as a matter of law. Applicants turn to *In re O’Farrell*, 7 USPQ2d 1673 (Fed. Cir. 1988), which held that, in order for a reference or references to obviate an invention, it must be shown that the reference (or references) contains:

- (1) detailed enabling methodology for practicing the claimed invention;
- (2) a suggestion for modifying the prior art to practice the claimed invention; and
- (3) evidence suggesting that the invention would be successful.

It is submitted that Anderson *et al.* would clearly fail to satisfy this tripartite test of *O’Farrell*. In particular, for the reasons discussed above, Anderson *et al.* does not provide any

reasonable expectation that such a combination would be successful and they fail to provide detailed enabling methodology for practicing the claimed invention, *e.g.*, for constructing the claimed conjugate. Moreover, there is no evidence that such a conjugate, once constructed, would actually function appropriately as an imaging agent.

In *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), the Federal Circuit took the *O'Farrell* doctrine a step further. In *Vaeck* the Federal Circuit stated that in order for an Examiner to make out a *prima facie* case of obviousness, three things must be shown:

- (1) that the prior art references teach or suggest each limitation of the claimed invention;
- (2) that the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition; and
- (3) that the prior art must demonstrate a reasonable expectation of success of the invention.

The court went on to emphasize that both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure. Here, for the reasons discussed above, we have neither. Thus, there is no *prima facie* case of obviousness based on *Anderson et al.*

3. Even if Auzeloux *et al.* Was Available as Prior Art, There Would be No *Prima facie* Case of Obviousness

It is the Examiner's responsibility to show that some objective teaching or suggestion in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art to combine the references to arrive at the claimed invention. *Pro-Mold & Tool Co. v. Great Lakes Plastics, Intl*, 745 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). In the absence of such a teaching or suggestion, there can be no *prima facie* case of obviousness. *See In re Vaeck*, 20 USPQ2d 1438.

There is no *prima facie* case of obviousness because the Examiner has not set forth any suggestion or motivation to one of ordinary skill in the art to combine reference teachings to lead to the claimed invention. As discussed above, the discussion of which is incorporated into this section, Anderson *et al.* provides no motivation to conjugate a targeting ligand to a radiolabeled BAT-dicarboxylic acid, or any reasonable expectation of success. The Examiner, however, has identified no such motivation in Auzeloux *et al.* to remedy the deficiency of Anderson *et al.* As admitted by the Examiner, “Auzeloux *et al.* **does not disclose a dicarboxylic acid containing BAT moiety.**” Office Action, page 4 (emphasis added). In the absence of any teaching or disclosure pertaining to any BAT-dicarboxylic acid, it is unlikely that one of ordinary skill in the art would find any motivation in this reference to provide for conjugation of any targeting ligand to a dicarboxylic acid.

Auzeloux *et al.* is cited by the Examiner “for its teachings that labeled BAT imaging agents may be used to evaluate tumors in locations such as the liver, lung, and brain.” Office Action, page 4. The radiolabeled molecules set forth in Auzeloux *et al.* do not appear to be conjugated to any targeting ligand. Further, the Examiner has not cited any particular disclosure in Auzeloux *et al.* pertaining to any targeting ligand. Therefore, Auzeloux *et al.* fails to remedy the deficiencies of Anderson *et al.*

4. Conclusion

In view of the above, it is respectfully submitted that the rejection of claims 52-58, 61-66, 69, and 79 under 35 U.S.C. §103(a) as being unpatentable over Anderson *et al.* in view of Auzeloux *et al.* should be withdrawn.

C. Conclusion

Applicants believe that the present document is a full and complete response to the Office Action dated April 19, 2006. Applicants submit that, in light of the foregoing remarks, the

present case is in condition for allowance. Should the Examiner have any question, please contact the undersigned below at 512-536-5639.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Monica De La Paz", with a long horizontal flourish extending to the right.

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